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EXAMINER
WOODWARD, CHERIE MICHELLE

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	**Application No.** 10/679,201	**Applicant(s)** DINARELLO ET AL.
	Examiner Cherie M. Woodward	**Art Unit** 1647

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7 and 9-40* is/are pending in the application.
  4a) Of the above claim(s) *12-40* is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *1-7,10 and 11* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.
10)☒ The drawing(s) filed on *3 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.
  Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
  Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
  a)☐ All b)☐ Some * c)☐ None of:
    1.☐ Certified copies of the priority documents have been received.
    2.☐ Certified copies of the priority documents have been received in Application No. _____.
    3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
  * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
  Paper No(s)/Mail Date *8/9/04, 10/4/04*.
4) ☐ Interview Summary (PTO-413)
  Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of claims 1-11 (Group 1) in the reply filed on 16 March 2006 is acknowledged. The traversal is on the grounds that Group I (claims 1-7 and 10-11) and Group II (claims 12-22) relate to the administration of "the effective amount of the cytokine-1 to bind the cytokine-2 receptor." Applicants argue that the only difference is the way of administration. This is not found persuasive because the claims of Group I are drawn to methods of treating or inhibiting disease comprising administering a cytokine-1 polypeptide to bind to the cytokine-2 receptor. Whereas, Group II, encompasses claim 12 and its dependent claims (13-22), which are drawn to a method of treating or inhibiting disease comprising administration of a vector encoding a cytokine and capable of expressing a cytokine-1. As such, the claims of Group II read on gene therapy. Methods of gene therapy are patentably distinct from methods of protein therapy. They require separate searches and have acquired a separate status in the art because of their recognized divergent subject matter. As such, the requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-7 and 10-40 are pending. Claims 8 and 9 have been cancelled by Applicants. Claims 12-40 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-7 and 10-11 are under examination.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted on 9 August 2004 and 4 October 2004 have been considered by the examiner. The Japanese language version of the Kashiwamura et al., reference was lined through because a translation was required. However, the translation is acknowledged and the reference to the translation has been initialed. Signed copies are attached.

4. The use of the trademarks BIACORE (p. 4, paragraph 0012), EXPASY (p. 21, line 1), CLONTECH, GENBANK, and GIBCO (p.38, paragraph 00135), and FICOLL-HISTOPAQUE (p. 40,

line 5) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, First Paragraph
Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-7 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for using IL-1F7b, IL-18R, and IL-18BP, in a method for treating an inflammatory disease, does not reasonably provide enablement for the method of using other IL-1 family members as cytokine-1 or cytokine-2 receptor proteins, nor other cytokine ligands or receptors in the treatment of a disease, other than rheumatoid arthritis (RA), ulcerative colitis (UC), or Crohn's disease (CD), that is caused or enhanced by induction of a cytokine-2 receptor. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor in a patient, the cytokine-2 being a member of the IL-1 family, the method comprising administration of an effective amount of a cytokine-1 to bind to the cytokine-2 receptor; wherein the cytokine-1 is an isoform, mutein, fused protein, or fragment thereof able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; wherein the cytokine –1 belongs to the IL-1 family; wherein the cytokine-2 receptor is IL-18R; wherein the disease is an inflammatory disease; wherein the cytokine-1 is administered systemically, subcutaneously, or intramuscularly; wherein the IL-18BP or mutein, fused protein, functional derivative or fragment thereof is further administered.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The invention is directed to a method of treating or inhibiting a disease that is caused by induction of a cytokine receptor, preferably belonging to the IL-1 family, comprising administering an effective amount of a different cytokine to bind the first. The state of the prior art is such that methods of treating chronic and acute inflammation with IL-1F7b (also known as IL-1H4, see, i.e. specification at p. 23, paragraph 0085), administered by parenteral, subcutaneous, or intramuscular injection (see WO 2001/40247, discussed in detail below), is known in the art. However, not all cytokine-1 proteins nor cytokine-2 receptors are known in the art. Additionally, not all diseases are known which may be caused by or enhanced by induction of a cytokine-2 receptor of the IL-1 family.

Enablement must be provided by the specification unless it is well known in the art. In re Buchner 18 USPQ 2d 1331 (Fed. Cir. 1991). The instant disclosure provides working examples of IL-1F7b, as the cytokine-1, and IL-18R, as the cytokine-2. However, only in vitro data is provided in the working examples. No working examples are provided showing the use of the IL-1F7b and IL-18R proteins in vivo. The instant disclosure also recites other examples of the generically claimed cytokine-1 and cytokine-2 receptors that may be used in the claimed method (see, i.e. p. 30, paragraph 00103). However, these examples are given by way of preferred exemplifications only and no other guidance or working examples are provided. It is well known in the art that cytokine interactions of one cytokine are not predictive of the functions of other cytokines, even members of the same cytokine family.

The assertion that all cytokine-2 receptors of the IL-1 family have biological activities similar to known IL-18R cannot be accepted in the absence of supporting evidence, because the relevant literature reports examples of polypeptide families wherein individual members have distinct, and sometimes even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). In the transforming growth factor (TGF) family, Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF- 1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. As such, the lack of direction or guidance present in the instant disclosure and the absence of working examples directed to in vivo studies or to any of the other recited cytokine-1 and cytokine-2 proteins (see specification, p. 30, paragraph 00103) is insufficient to permit one of ordinary skill to make and/or use the claimed invention in its full scope.

The claims also embrace a broad class of structural fragments and functional derivatives that are not taught in the specification. Therefore, the skilled artisan is not provided with sufficient guidance to use the claimed generic cytokine-1 polypeptides and claimed cytokine-2 receptors for the method of treating a disease. , the disclosure does not reasonably provide enablement for a cytokine-1 protein isoforms, muteins, fused proteins, or fragments thereof, able to bind IL-18BP; and IL-18BP or muteins, fused proteins, functional derivatives, or fragment thereof. There is no guidance or teaching in the specification as to the structure of any isoforms, muteins, or fusion proteins. Similarly, there is no teaching related to whether these isoforms, muteins, or fusion proteins should retain function. Although the term "functional derivatives" is defined in the specification (p. 29, paragraph 0099), but no guidance is provided as to which function(s) are referred to. The specification recites that functional derivatives "cover derivatives of cytokine-1...their muteins and fused proteins...which may be prepared from side chains "as long as they remain pharmaceutically acceptable, i.e. they do not destroy the activity of the protein which is substantially similar to the activity of IL-1F7b and do not confer toxic properties on compositions containing it." The specification fails to provide any guidance on which cytokine-1/mutein/fusion protein structural derivatives are acceptable, which cytokine-1/mutein/fusion protein functional groups may be used, or which functional activities are to be preserved. The disclosure fails to provide guidance as to the structural or functional inclusions or limitations that can be made with the generic cytokine-1 polypeptides such that they would encompass "functional derivates." Further, the disclosure fails to provide sufficient guidance on how to make the claimed isoforms, muteins, fused proteins, or fragments thereof that are able to bind to IL-18BP, nor muteins, fused proteins, functional derivatives, or fragments of IL-18BP such that it can be determined how to use the claimed polypeptide components in the claimed method of treatment. Rather, the specification provides an invitation for further experimentation.

General guidance is given regarding how to make and test variants of any protein. The scope of the patent protection sought by Applicant as defined by the claim fails to correlate reasonably with the scope of enabling disclosure set forth in the specification for the following reasons. The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein with the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequences are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al, 1990, *Science* 247:1306-1310, especially p.1306, column 2, paragraph 2; Wells, 1990, *Biochemistry* 29:8509-8517). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing and screening for active protein variants, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

The specification recites that the invention relates to the use of a cytokine in the treatment or prevention of a disease which is caused or aggravated by inducing a cytokine-2 receptor (p. 22, paragraph 0083). The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor. As such, the term "inhibiting" can read on prevention. The skilled artisan cannot envision the prevention of a disease without knowing which disease is to be prevented or inhibited. Similarly, the skilled artisan cannot envision the prevention of a disease without known which cytokine-1 proteins or cytokine-2 receptors are involved in the disease. Prevention involves "attacking" the underlying cause of the disease; i.e., disrupting the mechanisms which give rise to it. The skilled artisan is aware that the causes of disease are multifactoral the cause of many diseases were unknown at the time of the invention herein. For purposes of enablement, the specification must provide reasonable detail in order for those skilled in the art to carry out the invention. In this case, the specification must disclose a means of inhibiting all diseases (as broadly claimed in claim 1 and all inflammatory diseases as claimed in claim 7) regardless of the underlying cause of that disease. The teachings of the specification do not enabled a person of ordinary kill in the art to make and use the claimed method of inhibition insofar as the inhibition involves prevention. Moreover, "[p]atent protection is granted only in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." Genentech Inc. v. Novo Nordisk A/S, 108 F.3d at 1366, 42 USPQ2d at 1005 (Fed. Cir.), cert. denied, 118 S. Ct. 397 (1997), ("Tossing out the mere germ of an idea does not constitute an enabling disclosure").

Due to the large quantity of experimentation necessary to determine which disease is caused by or enhanced by the induction of a cytokine-2 receptor, and which cytokine-1 binds to the cytokine-2 receptor such that it can be determined how to use the claimed polypeptides in the claimed method of treatment, the lack of direction/guidance presented in the specification regarding same, the absence of in vivo working examples directed to same, the complex nature of the invention, and the breadth of the claims which fail to recite particular diseases, cytokines, or receptors and also embrace a broad class of structural fragments and functional derivatives, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, First Paragraph
Written Description

7. Claims 1-7 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor in a patient, the cytokine-2 being a member of the IL-1 family, the method comprising administration of an effective amount of a cytokine-1 to bind to the cytokine-2 receptor; wherein the cytokine-1 is an isoform, mutein, fused protein, or fragment thereof able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; wherein the cytokine –1 belongs to the

IL-1 family; wherein the cytokine-2 receptor is IL-18R; wherein the disease is an inflammatory disease; wherein the cytokine-1 is administered systemically, subcutaneously, or intramuscularly; wherein the IL-18BP or mutein, fused protein, functional derivative or fragment thereof is further administered.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a disease caused by the induction of a cytokine-2 receptor.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(1), the court states, "An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is are four single species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* rheumatoid arthritis (pp.9-11), Crohn's disease (pp. 11-14), ulcerative colitis (pp. 11-14), and psoriasis (p. 16) are disclosed in the specification, but are not claimed. Only a generic group of inflammatory diseases is claimed in claim 7. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. The term "a disease," in claim 1 and its dependent claims, encompasses all diseases that are caused by or enhanced by a cytokine-2 receptor. Applicants have not adequately described all diseases in any species that are caused or enhanced by the induction of a cytokine-2 receptor.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a disease caused by the induction of a cytokine-2 receptor. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

8. Claims 1-7 and 10-11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor in a patient, the cytokine-2 being a member of the IL-1 family, the method comprising administration of an effective amount of a cytokine-1 to bind to the cytokine-2 receptor; wherein the cytokine-1 is an isoform, mutein, fused protein, or fragment thereof able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; wherein the cytokine –1 belongs to the IL-1 family; wherein the cytokine-2 receptor is IL-18R; wherein the disease is an inflammatory disease; wherein the cytokine-1 is administered systemically, subcutaneously, or intramuscularly; wherein the IL-18BP or mutein, fused protein, functional derivative or fragment thereof is further administered.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claim indicates that these claims are drawn to a genus, i.e., a cytokine-2 receptor.

There is one species of the claimed genus disclosed that is within the scope of the claimed genus, *i.e.* IL-18 receptors. The disclosure of a single disclosed species may provide an adequate written description of a genus when the species disclosed is representative of the genus. However, the present claim encompasses numerous species that are not further described. The claims embrace cytokine-2 receptors of the IL-1 family and generic cytokine-1 polypeptides, as well as a broad class of structural fragments and functional derivatives that are not described in the specification. As such, Applicants have not adequately described all cytokine-2 receptors or cytokine-1 polypeptides, fragments or functional derivatives in any species.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a genus of cytokine-2 receptors. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

9. Claims 2 and 11 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The claims recite cytokine-1 protein isoforms, muteins, fused proteins, or fragments thereof, able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; and IL-18BP or mutein, fused protein, functional derivative, or fragment thereof. The specification fails to adequately describe all isoforms, muteins, fused proteins, or fragments of generic cytokine-1 proteins that are able to bind IL-18BP or an isoform, a mutein, fused protein, or fragments thereof. Additionally, the specification fails to adequately describe and IL-18BP muteins, fused proteins, functional derivatives, or fragments thereof.

In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus of isoforms, functional derivatives, fragments, muteins, and fused proteins. One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

10. Claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the

application was filed, had possession of the claimed invention. The claim recites the method of claim 1, wherein the cytokine-1 binds to the signaling chain of the cytokine-2 receptor. The disclosure fails to adequately describe a "signaling chain." The specification provides no description of the structure or function of the generically claimed cytokine-2 receptor such that a skilled artisan would recognize from the disclosure that the applicant was in possession of the genus of cytokine-2 receptor. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Claim Rejections - 35 USC § 112, Second Paragraph

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 2 and 11 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite cytokine-1 protein isoforms, muteins, fused proteins, or fragments thereof, able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; and IL-18BP or mutein, fused protein, functional derivative, or fragment thereof. No structural sequences of generic cytokine-1 proteins are disclosed such that the skilled artisan could determine the metes and bounds of isoforms, muteins, fused proteins or fragments that meet the limitations of the claims.

13. Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the method of claim 1, wherein the cytokine-1 binds to the signaling chain of the cytokine-2 receptor. The disclosure fails to teach what a "signaling chain" is or where it could be found on any given cytokine-2 receptor. The metes and bounds of a "signaling chain" are not disclosed.

Claim Rejections - 35 USC § 102

14. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

15. Claims 1-7 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Kumar et al., WO 2001/40247 A1 (international publication date 7 June 2001, priority to 1 December 1999). The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor in a patient, the cytokine-2 being a member of the IL-1 family, the method comprising administration of an effective amount of a cytokine-1 to bind to the cytokine-2 receptor; wherein the cytokine-1 is an isoform, mutein, fused protein, or fragment thereof able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; wherein the cytokine –1 belongs to the IL-1 family; wherein the cytokine-2 receptor is IL-18R; wherein the disease is an inflammatory disease; wherein the cytokine-1 is administered systemically, subcutaneously, or intramuscularly.

WO 2001/40247 teaches IL-1H4 as SEQ ID NO: 2, (also known in the art at IL-1F7b; see also specification p. 23, paragraph 0085) and is 99.9908% identical to instant SEQ ID NO: 6 (see also, NCBI accession number AF200496; the instant specification identifies IL-1F7b as accession number AF200496 (p. 21, paragraph 0073), and specification p. 4, paragraph 0012, which discusses amino acid polymophisms (V31 G and A42T) in IL-1F7b based on two base pair mutations in exon 2). WO 2001/40247 also teaches a method for using IL-1H4/IL-1F7b in the treatment of chronic and acute inflammation (p. 3, lines 1-14). Variants of IL-1H4/IL-1F7b are taught at page 18, lines 23-35. The IL-18 receptor is taught at page 2, lines 28-32. Administration is taught at page 12, lines 12-13, and includes parenterally, subcutaneous, and intramuscular injection.

16. Claims 1-7 and 10 are rejected under 35 U.S.C. 102(e) as being anticipated by McDonnell et al., US Patent 6,342,371 B1 (29 January 2002, priority date 16 April 1999). The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor in a patient, the cytokine-2 being a member of the IL-1 family, the method comprising administration of an effective amount of a cytokine-1 to bind to the cytokine-2 receptor; wherein the cytokine-1 is an isoform, mutein, fused protein, or fragment thereof able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; wherein the cytokine –1 belongs to the IL-1 family; wherein the cytokine-2 receptor is IL-18R; wherein the disease is an inflammatory disease; wherein the cytokine-1 is administered systemically, subcutaneously, or intramuscularly.

McDonnell et al., teach IL-1H4 as SEQ ID NO: 2, (also known in the art at IL-1F7b; see also specification p. 23, paragraph 0085) and is 99.9908% identical to instant SEQ ID NO: 6 (the instant specification identifies IL-1F7b as accession number AF200496 (p. 21, paragraph 0073); and specification p. 4, which discusses amino acid polymophisms (V31 G and A42T) exist in IL-1F7b based on two base pair mutations in exon 2). McDonnell et al., also teach a method for using IL-1H4/IL-1F7b in the treatment of chronic and acute inflammation (column 2, lines 41-61). Variants of IL-1H4/IL-1F7b are taught at column 15, lines 9-32. The IL-18 receptor is taught at column 2, lines 30-38. Administration is taught at column 10, lines 1-4, and includes parenterally, subcutaneous, and intramuscular injection.

Claim Rejections - 35 USC § 103

17. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

18. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claims 1-7 and 10-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over McDonnell et al., US Patent 6,342,371 B1 (29 January 2002, priority date 16 April 1999) and WO 2001/40247 A1 (international publication date 7 June 2001, priority to 1 December 1999; cited by Applicants in IDS of 9 August 2004), in view of Pan et al., (Cytokine 7 January 2001 13(1):1-7; cited by Applicants in IDS of 9 August 2004), in further view of Kumar et al., (Cytokine 21 April 2002 18(2):61-71; cited by Applicants in IDS of 9 August 2004).

The claims recite a method of treating or inhibiting a disease that is caused or enhanced by induction of a cytokine-2 receptor in a patient, the cytokine-2 being a member of the IL-1 family, the method comprising administration of an effective amount of a cytokine-1 to bind to the cytokine-2 receptor; wherein the cytokine-1 is an isoform, mutein, fused protein, or fragment thereof able to bind IL-18BP or an isoform, a mutein, fused protein, or fragment thereof; wherein the cytokine –1 belongs to the IL-1 family; wherein the cytokine-2 receptor is IL-18R; wherein the disease is an inflammatory disease; wherein the cytokine-1 is administered systemically, subcutaneously, or intramuscularly; wherein the IL-18BP or mutein, fused protein, functional derivative or fragment thereof is further administered.

WO 2001/40247 (discussed *supra*) teaches IL-1H4 as SEQ ID NO: 2, (also known in the art at IL-1F7b; see also specification p. 23, paragraph 0085) and is 99.9908% identical to instant SEQ ID NO: 6 (see also, NCBI accession number AF200496; the instant specification identifies IL-1F7b as accession number AF200496 (p. 21, paragraph 0073), and specification p. 4, paragraph 0012, which discusses amino acid polymophisms (V31 G and A42T) in IL-1F7b based on two base pair mutations in exon 2). WO 2001/40247 also teaches a method for using IL-1H4/IL-1F7b in the treatment of chronic and acute inflammation (p. 3, lines 1-14). Variants of IL-1H4/IL-1F7b are taught at page 18, lines 23-35. The IL-18 receptor is taught at page 2, lines 28-32. Administration is taught at page 12, lines 12-13, and includes parenterally, subcutaneous, and intramuscular injection.

McDonnell et al., (discussed *supra*) teach IL-1H4 as SEQ ID NO: 2, (also known in the art at IL-1F7b; see also specification p. 23, paragraph 0085) and is 99.9908% identical to instant SEQ ID NO: 6 (the instant specification identifies IL-1F7b as accession number AF200496 (p. 21, paragraph 0073); and specification p. 4, which discusses amino acid polymophisms (V31 G and A42T) exist in IL-1F7b based on two base pair mutations in exon 2). McDonnell et al., also teach a method for using IL-1H4/IL-1F7b in the treatment of chronic and acute inflammation (column 2, lines 41-61). Variants of IL-1H4/IL-1F7b are taught at column 15, lines 9-32. The IL-18 receptor is taught at column 2, lines 30-38. Administration is taught at column 10, lines 1-4, and includes parenterally, subcutaneous, and intramuscular injection.

Neither WO 2001/40247 nor McDonnell et al., teach the further administration of IL-18BP, or mutein, fusion protein, functional derivative, or fragment thereof.

Pan et al., teach IL-1HL (Figure 1B) that is 100% identical to IL-1F7b. Pan et al., also teach a IL-1H-IL-18R binding complex (Figures 4 and 5) and discusses its putative role in inflammation and immune responses (p. 6, first column, second paragraph). The role of IL-18BP in inhibiting binding to IL-18R is taught at p. 1, column 2, second paragraph.

Kumar et al., teach binding of IL-1F7b to IL-18R (p. 63, column 1, last paragraph to p. 64, column 2). IL-18BP is taught at p. 62, column 1, first paragraph. IL-18BP-Fc fusion protein is taught at p. 65, column 1, first paragraph.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to combine the teachings of WO 2001/40247 and McDonnell et al., with Pan et al., in view of Kumar et al., to use IL-1H4/IL-1HL/IL-1F7b in the treatment of an inflammatory disease caused or enhanced by induction of a cytokine-2 receptor in a patient, comprising the further administration of IL-18BP, or mutein, fusion protein, functional derivative, or fragment thereof. The person of ordinary skill in the art would have been motivated to make the modification because it was well known in the art that IL-18 induces interferon-γ production during inflammation and Pan et al., showed that IL-18BP inhibits binding to IL-18R in a manner similar to the way IL-1ra inhibits binding of IL-1 to the IL-1R. Kumar et al., determined that IL-18R, and various IL-18 receptor subunit fusion proteins, including IL-18Rα-Fc and IL-18BP-Fc, could be used in multiple binding assays to determine whether IL-1H4/IL-1F7b binding to a IL-18R, IL-18BP or IL-18Rα was involved in interferon-γ production or inhibition, and thus involved in pro-inflammatory processes through the interferon-γ pathway, as is typical of most IL-1-related proteins. Pan et al., taught that the IL-1H4/IL-1HL/IL-1F7b protein naturally binds to IL-18R. Both WO 2001/40247 and McDonnell et al., determined that the IL-1H4/IL-1F7b protein could be used in a method of treating an inflammatory disease. Thus, the person of ordinary skill in the art would have reasonably expected success in the treatment of an inflammatory disease caused or enhanced by induction of a cytokine-2 receptor in a patient, comprising the further administration of IL-18BP, or mutein, fusion protein, functional derivative, or fragment thereof, because it would be beneficial to use IL-18BP (as taught by Kumar et al.,) to slow or antagonize the binding of IL-1H4/IL-1HL/IL-1F7b to its natural binding partner, IL-18R (as shown by Pan et al.,).

Conclusion

NO CLAIM IS ALLOWED.

21. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CMW

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